Research Article

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The Laennec staging system for histological sub-classification of cirrhosis is useful for stratification of prognosis in patients with liver cirrhosis

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Backgrounds & Aims: The clinical severity of cirrhosis varies widely. We investigated whether histological sub-classification of cirrhosis using the Laennec system can discriminate different outcomes among patients with cirrhosis.

Methods: One hundred and seventy-five patients with chronic liver disease who underwent liver biopsy and showed stage 3 or 4 fibrosis between January 2001 and December 2008 were prospectively enrolled. Cirrhosis was sub-classified into three groups (4A, 4B, and 4C) according to the Laennec system. The end point was liver-related event (LRE) occurrence, including decompensation, hepatocellular carcinoma, and liver-related death.

Results: The median age of the patients (110 men, 65 women) was 55 years. Stages 3, 4A, 4B, and 4C were identified in 46 (26.3%), 16 (9.1%), 82 (46.9%), and 31 (17.7%) patients, respectively. During the follow-up period, LREs occurred in 32 (18.3%) patients: 4 (8.7%) with stage 3, 2 (12.5%) with stage 4A, 17 (20.7%) with stage 4B, and 9 (29.0%) with stage 4C. In a multivariate analysis, histological sub-classification of cirrhosis independently predicted LRE occurrence. While patients with stage 4A tended to be at higher risk of LRE occurrence than those with stage 3, patients with stages 4B and 4C had significantly higher risks of LRE occurrence, with hazard ratios of 6.158 ($p = 0.016$) and 8.945 ($p = 0.004$), respectively.

Conclusions: Histological sub-classification of cirrhosis using the Laennec system can be used to assess the risk of LRE occurrence among patients with cirrhosis. Our study provides a solid basis for further studies of non-invasive methods for monitoring the risk of LRE occurrence and will help physicians to establish optimum treatment strategies.

Keywords: Cirrhosis; Fibrosis; Laennec staging system; Liver biopsy; Liver-related event.

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Abbreviations: HCC, hepatocellular carcinoma; LRE, liver related event; LB, liver biopsy; TE, transient elastography; LS, liver stiffness; AFP, alpha-fetoprotein; HR, hazard ratio; CI, confidence interval; INR, international normalized ratio.

Introduction

Liver cirrhosis is histologically defined as a diffuse state with replacement of the normal lobular architecture by abnormal nodules and fibrous septa [1]. Although cirrhosis is widely considered to be an end-stage liver disease, clinical severity, and prognosis within this diagnosis vary widely [2]. Clinically, cirrhosis can be categorized into compensated and decompensated states [3]. While this approach may give a clear indication for liver transplantation [4], it is of no use in predicting the development of hepatic decompensation. Furthermore, it does not provide prognostic information for the bulk of cirrhotic patients who are compensated and might benefit from tailored management to prevent decompensation. Therefore, the identification of prognostic factors to predict the development of liver-related events (LREs), such as hepatic decompensation, hepatocellular carcinoma (HCC), and liver-related mortality in patients with compensated cirrhosis is important.

Among the characteristics of patients with compensated cirrhosis, the degree of liver fibrosis on biopsy may be important for predicting the development of hepatic decompensation. However, currently used histological staging systems, such as the Ishak [5], METAVIR [6], and Batts systems [7], group all patients with cirrhosis into a single category without taking account the severity of cirrhosis. Furthermore, because recent antiviral and anti-fibrotic treatments can contribute to the regression of fibrosis in patients with histological cirrhosis [8–10], the simple one-stage description for cirrhosis is not able to stratify patients for

treatment assignment or evaluation of treatment response [3]. Thus, a more refined histological sub-classification of cirrhosis is needed [11].

The Laennec staging system, a modification of the METAVIR system, was proposed to meet this need [12,13]. This system subdivides cirrhosis into three groups (4A, 4B, and 4C) based on the thickness of the fibrous septa and the size of nodules. Although recent cross-sectional studies reported the usefulness of the Laennec system in correlating clinical stage and grade of portal hypertension [12,14], no prospective longitudinal study has documented the predictive values of the Laennec system using LRE occurrence, including hepatic decompensation, HCC, and liver-related death, as solid end points. In this study, we evaluated the Laennec staging system for predicting LRE occurrence in patients with cirrhosis and therefore stratifying these patients according to prognosis.

Patients and methods

Patients

Between January 2001 and December 2008, a total of 712 patients with chronic hepatitis who underwent liver biopsy (LB) at Severance Hospital, Yonsei University College of Medicine, Seoul, Korea were consecutively enrolled in this prospective study. Informed consent was obtained from all patients before enrollment. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the institutional review board of our institute.

Because we planned to calculate the relative risk of LRE occurrence in patients with cirrhosis (stage 4A, 4B, or 4C), as compared to stage 3, we first excluded 481 patients with Laennec stage 0–2 on biopsy and a further 56 patients if the biopsy was less than 10 mm in length or if other exclusion criteria were present. The remaining 175 patients with stage 3, 4A, 4B, or 4C were selected for statistical analysis (Supplementary Fig. 1).

Liver biopsy and histological assessment

The indication of LB was to assess the severity of liver fibrosis and necroinflammation. LB was performed before starting antiviral treatment, especially in patients with chronic hepatitis B or C virus infection. All patients underwent ultrasound-guided percutaneous LB. LB specimens were formalin fixed and paraffin embedded. Then, 4-μm-thick sections were stained with hematoxylin-eosin and Masson's trichrome. All liver tissue samples were evaluated by an experienced hepatopathologist (Y.N. Park) who had no access to clinical data for the study population.

The degree of liver fibrosis was evaluated semi-quantitatively according to the Laennec system (Supplementary Fig. 2) [13]. Fibrosis was first scored as follows: 0, no definite fibrosis; 1, minimal fibrosis (no septa or rare thin septum; may have portal expansion or mild sinusoidal fibrosis); 2, mild fibrosis (occasional thin septa); 3, moderate fibrosis (moderate thin septa; up to incomplete cirrhosis); and 4, cirrhosis. Stage 4 was distinguished from stage 3 by more numerous septa per unit length of biopsy sufficient to display nodules with rounded contours. Then, stage 4 was sub-classified into three groups: 4A, mild cirrhosis, definite or probable; 4B, moderate cirrhosis (at least two broad septa); and 4C, severe cirrhosis (at least one very broad septum or many minute nodules). The terms 'broad septum' and 'very broad septum' were defined by comparing the relative thickness of fibrous septa and sizes of nodules [14]. Activity grade (degree of necroinflammatory activity in the lobules and periportal area) was scored as follows: A0, none; A1, mild activity; A2, moderate activity; and A3, severe activity. Activity grade was defined as lobule or periportal activity, whichever was the higher.

The median length of biopsies in the study set was 16 mm (range, 10–25 mm). The mean biopsy length of each fibrosis stage was statistically equivalent (15.0 ± 3.6, 16.1 ± 3.1, 16.0 ± 3.2, and 16.6 ± 3.5 mm in stages 3, 4A, 4B, and 4C, respectively; all p >0.05 among fibrosis stages).

Morphometry

Morphometry was performed as described [15,16]. Briefly, trichrome-stained sections of all liver biopsies were examined without knowledge of the histological score. Digital images of 1–4 fields of each biopsy were captured at a final magnification of 20×. The thickness of the fibrous septa and the size of the nodules (maximum distance between two adjacent septa) were measured and the mean value of each case was calculated.

Measurement of liver stiffness values

After transient elastography (TE) using FibroScan® (EchoSens, Paris, France) was introduced in our institute, liver stiffness (LS) values by TE were obtained for all patients who underwent LB. LS measurement using TE was performed according to the manufacturer's recommendations [17]. All LS measurements were obtained by one experienced technician who was blinded to the clinical and histologic data. In this study, only LS values with at least 10 validated measurements and a success rate of at least 60%, and interquartile range to median value ratio less than 0.3, were considered reliable. The median interval between TE and LB was 12 (range, 0–18) days.

Laboratory tests

In addition to demographic data, the following laboratory parameters were measured at the time of LB: serum albumin level, total bilirubin, aspartate aminotransferase, alanine aminotransferase, alpha-fetoprotein (AFP), prothrombin time, and platelet count.

Follow-up

Each patient was screened for HCC by ultrasonography at their initial visit. Six patients were excluded due to the presence of HCC at enrollment. If no evidence of HCC was found, patients were subjected to periodic surveillance by ultrasonography and laboratory tests, including measurement of AFP levels every 3 or 6 months. Furthermore, the development of hepatic decompensation was monitored during the study period. If LREs occurred, patients were admitted for immediate and appropriate management. The last follow-up month of our study was April 2011 and the median follow-up duration was 52.4 (range, 9.7–125.2) months. The follow-up duration was similar among fibrosis stages (69.2 ± 30.2, 51.6 ± 11.7, 51.2 ± 15.0, and 54.2 ± 20.1 months in stage 3, 4A, 4B, and 4C, respectively; all p >0.05).

Definitions of liver-related events

The primary end point was LRE occurrence, defined as a cirrhosis-related complication including hepatic decompensation, HCC, and liver-related death. Hepatic decompensation comprised ascites, variceal bleeding, hepatic encephalopathy, spontaneous bacterial peritonitis, and hepatorenal syndrome. Ascites was diagnosed clinically and was confirmed by ultrasonography or computed tomography [18]. Variceal bleeding was diagnosed endoscopically [19]. Hepatic encephalopathy was diagnosed based on the presence of temporospatial disorientation, altered level of consciousness, or asterixis in the absence of other possible causes [20]. Spontaneous bacterial peritonitis (SBP) was defined as an ascitic fluid infection without an apparent intra-abdominal surgically treatable source with confirmation by culture and an elevated ascitic fluid absolute polymorphonuclear leukocyte count ($\geqslant$250 cells/mm^3) [21]. Hepatorenal syndrome was diagnosed when acute renal failure developed in association with advanced chronic liver disease, after exclusion of other causes of renal failure [22].

For patients enrolled before 2005, diagnosis of HCC was based on the guidelines of the European Association for the Study of the Liver (EASL) [23]. Briefly, for nodules larger than 2 cm, HCC can be diagnosed by the coincident findings from at least two imaging techniques showing typical features of arterial hypervascularization, or findings from one imaging technique and an AFP level of >400 ng/ml. For nodules between 1 and 2 cm in size, biopsy is recommended. For patients who were enrolled after 2005, HCC was diagnosed based on the guidelines of the American Association for the Study of Liver Diseases (AASLD) [24]. Briefly, for tumors larger than 2 cm, HCC was diagnosed when typical features of HCC were detected (hypervascularity and washout in the portal/venous phase) by one dynamic imaging technique and the AFP level was >200 ng/ml. For nodules between 1 and 2 cm in size, it was necessary to detect typical features of HCC using two dynamic imaging techniques. For tumors smaller than 1 cm, ultrasonography was repeated after 3 months.

Liver-related deaths included death caused by hepatic failure (regardless of etiology), HCC progression, variceal bleeding, and acute infections such as SBP [25].